REMARKS/ARGUMENTS

Status of the Claims

With this amendment, claims 2 and 13-16 are pending and under examination in this application. Claims 1 and 3-11 are withdrawn from consideration as being non-elected subject matter subject to Applicants' election in the response filed on November 16, 2007. Claim 12 has been cancelled without prejudice. All of the amendments are discussed in the following comments.

Amendments to the Specification

As noted by the Examiner in the Office Action, the specification has been amended to correct an inadvertent grammatical error on page 11, lines 5-7 of the application as filed, which corresponds to the second sentence of paragraph [0056] on page 5 of the published application, U.S. Patent Application Publication No. 2006/0183225 (hereafter "the '225 Publication").

As noted by the Examiner in the Office Action, the specification also has been amended to spell out the first encounter of the abbreviation "TSA" on page 5, line 21 of the application as filed, which corresponds to paragraph [0026] on page 2 of the '225 Publication. Support for this amendment may be found, for example, in the title of Embodiment 2 that is between paragraphs [0061] and [0062] on page 5 of the '225 Publication.

No new matter is introduced. Entry of the amendments is respectfully requested.

Claim Amendments

Reconsideration of this application is respectfully requested. Applicants have amended claims 2, 13, 15, and 16. Claim 2 has been amended to recite "chicken-derived B cells" rather than "immunocytes" and to recite that the chromatin structure of chromosomes is relaxed "with a histone deacetylase inhibitor." Support for these amendments may be found, for example, on page 2, paragraphs [0020] and [0021] of the '225 Publication. Claim 13 has been amended to change its dependency from claim 12 to claim 2. Claim 15 has been amended to insert a comma after recitation of "Claim 2." Claim 16 has been amended to recite "chicken-derived B cells" rather than "immunocytes" and to recite that the chromatin structure of chromosomes is relaxed "with a histone

deacetylase inhibitor." Support for these amendments may be found, for example, on page 2, paragraphs [0020] and [0021] of the '225 Publication. Claim 16 also has been amended to correct the antecedent basis for "target antigen" by specifying "a target antigen" in the preamble and "said target antigen" in part ii) of claim 16. No new matter has been introduced.

Claim 12 has been cancelled without prejudice. Applicants expressly reserve the right to pursue any cancelled subject matter in subsequent applications that claim benefit from this application. Entry of the amendments and reconsideration of the pending claims is respectfully requested.

Information Disclosure Statement (IDS)

In the Office Action, the Examiner has commented that Reference 1 of the 08-02-2007 IDS was not considered due to "absence of a publication". Additionally, the Examiner states that in the 01-09-2007 IDS, Reference CA was not considered because an English-language abstract or translation of the document was not provided.

Applicants respectfully disagree with the Examiner regarding Reference 1 of the 08-02-2007 IDS. The Examiner's attention is directed to the copies of Reference 1 and PTO/SB/08A as filed in the IDS dated 08-02-2007 (see Tab 1 enclosed herewith). The copy of Reference 1 that was filed on 08-02-2007 has an English-language abstract that satisfies the disclosure requirement for concise explanation of relevance of non-English language information under 37 C.F.R. § 1.56(c).

With respect to Reference CA of the 01-09-2007 IDS, Applicants provide on the IDS that is filed herewith a concise, English-language explanation of Reference CA, which complies with 37 C.F.R. § 1.56(c).

Accordingly, it is respectfully requested that the Examiner enter and consider References 1 and CA, as well as the other references cited in the IDS that is filed herewith and that are discussed in the following comments, and that these references be listed on the face of any a patent issuing from the current application.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 2 and 12-16 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. The Examiner acknowledges that the specification is enabling for a method of producing antibodies comprising enhancing DNA homologous recombination at an antibody locus, wherein DNA homologous recombination is occurring at the locus using the chicken DT40 B-cell line by relaxing the chromatin structure of chromosomes with trichostatin in said immunocytes, and thereby obtaining diverse antibodies. However, the Examiner states that the specification is not enabling for a method of producing antibodies comprising enhancing DNA homologous recombination at an antibody locus, *e.g.*, Ig, in any immunocyte cell line other than in the chicken DT40 B-cell by relaxing the chromatin structure. The Examiner asserts that in part because "the word immunocyte is not defined in the as-filed specification" the pending claims encompass a genus of eukaryotic immunocytes for which a skilled worker would have to study and test for homologous recombination abilities. Moreover, the Examiner asserts that no other mechanisms of relaxing the chromatin are disclosed other than using trichostatin A. Applicants traverse.

First, the Examiner's attention is respectfully directed to page 7 of the English-language specification, as filed (see also paragraph [0043] on page 3 of the '225 Publication), which defines the term "immunocyte" as "B cells that have antibody production ability." Second, in order to expedite prosecution of the present case, and without conceding the Examiner's position or the validity of the rejection, Applicants have amended claims 2, 13, 15, and 16 and cancelled claim 12, without prejudice, as discussed in the foregoing comments, to more particularly point out and distinctly claim the subject matter being prosecuted.

With respect to the Examiner's assertion that only trichostatin A is enabled, the Examiner's attention is respectfully directed to paragraph [0047] of the '225 Publication that recites:

> As the "histone deacetylase inhibitor," it is thought that any such inhibitor is usable as long as it is known by persons skilled in the art, such as protein factors such as antibodies that have histone deacetylase (HDAC) activity suppressing

> activity, trichostatin A, and small molecule compounds such as butylate and valproate, but most preferably, trichostatin A is utilized.

Based upon the teachings of the specification as filed and his own general knowledge, a skilled worker would know that he or she could interchangeably use any histone deacetylase inhibitor, not only trichostatin A, in the claimed methods. Accordingly, based upon the foregoing comments, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

Rejections under 35 U.S.C. § 103, Obviousness

Claims 2[1] and 15 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Sonoda et al., 2001, *Phi. Trans. R. Soc.* London, 2001, 11-117 (hereafter "Sonoda"), in view of McMurry et al, 2000, *Science* 495-498 (hereafter "McMurry") and further in view of Watson, et al., 2001, *Recombinant DNA*, pp. 297-304 (hereafter "Watson"). The Examiner states that the manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology, and a skilled worker at the time the invention was made would have been motivated to combine Sonoda, McMurry, and Watson with a reasonable expectation of success to improve the production of antibodies by homologous recombination by allowing accessibility of recombinant enzymes to regulate V(D)J recombination.

The Examiner states that Sonoda teaches the use of the chicken B-lymphocyte line DT40 for the production of diverse antibodies and that Sonoda discloses that efficient homologous recombination is an intrinsic characteristic of primary chicken B lymphocytes. The Examiner also states that Sonoda teaches that the lymphocyte line DT40 exhibits Ig conversion by nucleotide sequence blocks derived from V region pseudogenes that are transferred to functional rearranged V(D)J segments. The Examiner is of the opinion that the teachings indicate that the B-lymphocyte line DT40 undergoes rearrangement of antibody chains by homologous recombination of the chicken Ig loci to generate diversity. However, the Examiner acknowledges that Sonoda does not

[1] In the Office Action, the Examiner inadvertently refers to claims 1 and 15, however claim 1 is currently withdrawn and not under examination. During a May 2, 2008 telephone conversation with Examiner Leavitt, Applicants's reprepsentatives, Andrew K. Holmes and Shilpa V. Patel, Examiner Leavitt confirmed that she had intended to reject claims 2 and 15.

specifically teach enhancing homologous recombination by relaxing the chromatin. For this, the Examiner relies upon McMurry as teaching a role for histone acetylation in the developmental regulation of V(D)J recombination. The Examiner acknowledges that Sonoda and McMurry do not specifically disclose that regulation of V(D)J recombination is the same in T cells and immunocytes. For this teaching, the Examiner relies upon Watson as disclosing that recombination of the V, D, J and C segments in T cell receptor genes is similar to the recombination of the antibody V(D)J genes and, therefore, one of ordinary skill in the art would have found it obvious to improve the production of antibodies by homologous recombination by allowing accessibility of recombinant enzymes to regulate V(D)J recombination. Applicants respectfully disagree with the Examiner.

Obviousness requires that each and every claim limitation be disclosed or suggested by the prior art. M.P.E.P § 2143.01.

The methods called for in the present claims encompass a method of antibody production comprising enhancing DNA homologous recombination at an antibody locus when producing antibodies from chicken-derived B cells in which DNA homologous recombination is occurring by relaxing with histone deacetylase inhibitor the chromatin structure of the chromosomes in the chicken-derived B cells to obtain diverse antibodies. The pending claims also encompass a method for producing an antibody which can bind to a target antigen. *No combination of the cited references teaches or suggests the combination of uses and features, called for in the pending claims.*

At the outset, it is respectfully pointed out that Sonoda, as acknowledged by the Examiner, does not teach or suggest homologous recombination by relaxing the chromatin. Furthermore, a skilled artisan would not have been able to predict the precise manner in which the elements that the Examiner points to in the cited prior art should have been combined to arrive at the claimed methods because V(D)J recombination and homologous recombination are different mechanisms. Specifically, the skilled artisan would not have looked to the teachings of Watson or McMurry, to which the Examiner points, for guidance to arrive at the claimed methods because V(D)J recombination (in both B cells and T cells) and homologous recombination are different mechanisms.

As described by Jones and Gellert (2004, *Immunol. Rev.*, 200:233-248) and Bassing et al. (2002, *Cell*, v.109 Suppl: 44-55) (copies filed herewith in IDS referred to in the foregoing comments), the basic molecular mechanisms for V(D)J recombination are entirely different from homologous recombination (also known as gene conversion). V(D)J recombination requires functions of a "site-specific endonuclease", called RAG1-RAG2, which triggers DNA break formation by a mechanism similar to the mechanism of transposition, in addition to other factors such as Ku and Artemis. On the other hand, the mechanism of gene conversion requires activation induced cytidine deaminase (AID) and other factors involved in homologous recombination (*e.g.*, XRCC3).

Moreover, regarding V(D)J recombination, it was thought that histone acetylation would not be sufficient for relaxation of chromatin. Thus, Bassing et al. (2002) teaches away from the use of histone acetylation to enhance gene conversion. *See also*, McMurry and Senoo et al. 2001, *Int. Immunology*, 12(11): 1405-1414 (copy filed herewith in IDS referred to in the foregoing comments), both of which are cited by Bassing et al (2002). Thus, one of ordinary skill in the art would not have been motivated to use histone acetylation to enhance gene conversion.

Taken together, a skilled worker at that time of filing of the priority document of the current application would not have looked to Watson or McMurry for guidance about enhancing homologous recombination because these references teach only enhancement of a different and unrelated mechanism, V(D)J recombination. Thus, a skilled artisan would not have had an expectation of success based upon the teachings of Watson or McMurry that gene conversion (*i.e.*, homologous recombination) in chicken-derived B cell lines *e.g.*, DT-40 cells) could have been enhanced by hyperacetylation of histones using a histone deacetylase inhibitor (*e.g.*, trichostatin (TSA)). Furthermore, neither Watson nor McMurry teach or suggest that studies using V(D)J recombination would produce predictable results if the mechanism of homologous recombination is used instead.

Additionally, it is respectfully pointed out that the state of the art at the time of filing of Japanese patent application no. JP 2002-221232, which is the priority application of the current application undergoing prosecution, provided no guidance or expectation of success for designing or

using the claimed methods to prepare diverse antibodies including antigen-specific antibodies from DT40 cells. The differences between the prior art and the pending claims are significant because the prior art provides no guidance or expectation of success for making or using the methods as called for by the present claims; and the level of ordinary skill in this art is relatively high. *See KSR Int'l Co. v. Teleflex Inc.*, 127 s. Ct. 1727, 1734 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15-17 (1966). The guidance that is missing in the cited prior art documents is found in the teachings of the present invention (*See* Embodiments 1-4 of the '225 publication) as well as the teachings of Seo H., et al. 2005, *Biotechnology*, vol. 23: 731-735 (copy filed herewith with IDS referred to in the foregoing comments), a publication, by the named inventors of the current application, that was published after the filing date of the current application and describes the surprising results of the current invention. For the reasons set forth above, even with Sonoda, McMurry, and Watson in hand one of ordinary skill would have been unable to predict that the method of antibody production called for in the present claims would obtain a diverse population of antibodies. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

Claims 12-14 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonoda, McMurry, Watson, and further in view of Choy et al. (2002, Mol Cell Biol., 8215-8225; hereafter "Choy").

The Examiner attempts to cure the deficiencies of the cited prior art discussed above with Choy. However, nothing in Choy, alone or in combination with the other cited prior art references, describes or suggests the claimed methods for antibody production. Choy teaches transcription of a gene. One of ordinary skill in the art, when looking for a method of enhancing homologous recombination during antibody production, would not seek guidance from a reference relating to a non-analogous art, *i.e.*, gene transcription. Thus, a skilled worker would look to Choy for such guidance. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

Claim 16 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Sonoda, McMurry, Watson, and further in view of Sale et al., U.S. Patent 7,122,339 (hereafter "Sale").

The examiner attempts to cure the deficiencies of the cited prior art discussed above with sale. However, nothing in Sale, alone or in combination with the other cited prior art references, describes or suggests the claimed methods. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

Determining the various elements that can be combined to design a method suitable for diverse antibody production using DNA homologous recombination by relaxing with a histone deacetylase inhibitor the chromatin structure of chromosomes requires experimentation and is unpredictable until a method of that type is designed and used. It was only through experiments carried out by the present inventors as described in the specification that the parameters for the inventive methods were determined and tested. MPEP § 2145(X)(B); *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988)

Finally, this conclusion is consistent with the Supreme Court decision *KSR v. Teleflex*, 127 S. Ct 1727 (2007)[2] where in contrast to the presently claimed methods, the court discussed *predictable* outcomes that support a finding of obviousness stating:

> The combination of familiar elements according to known methods is *likely to be obvious when it does no more than yield predictable results.*" (emphasis added) (discussing *United States v. Adams*, 383 U.S. 39, 40 (1966) (the companion case to *Graham*), *Anderson's Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

As discussed in the foregoing comments, the Examiner attempts to combine disparate teachings in the prior art to which a skilled worker would not have looked to guidance in arriving at the claimed methods because the mechanisms of V(D)J recombination and homologous recombination are different. As such, a skilled worker would not have had an expectation of success or predictable results if he or she combined the cited prior art.

For at least the reasons set forth above, pending claims 2 and 15 are not obvious over the prior art of record. Reconsideration of the claims and withdrawal of the rejections under 35 U.S.C.§ 103(a) is respectfully requested.

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[2] Holding that *Graham v. John Deere* controls the obviousness inquiry and warning that a rigid application of the teaching / suggestion / motivation test as a litmus test for obviousness is inconsistent with the *Graham* framework.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By_____

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TAB 1